Comparison of Racemization Processes in 1-Arylpyrimidine-2-thione and 3-Arylthiazoline-2-thione Atropisomers and Their Oxygen Analogues

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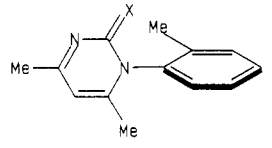
1-(2′-Methylphenyl)-4,6-dimethylpyrimidine-2-thione (**1a**), its oxygen analogue (**1b**) and a series of *N*-aryl-4-methylthiazoline-2-thiones **2a–5a** and -2-ones analogues **2b–5b** have been separated into atropisomers by liquid chromatography on CSP microcrystalline cellulose triacetate, owing to the hindered rotation around the N sp^2–C_{aryl} sp^2 bond. Racemization energies have been determined in diglyme when possible. The inspection of X-ray structure determination for compounds **1a** and **3a**, as well as the consideration of direct and buttressing steric effects on the barrier energies and comparison with model compounds, suggests that the racemization in pyrimidine derivatives occurs through a ring opening–ring closure reaction whereas the internal rotation around the N sp^2–C_{aryl} sp^2 accounts for the observed racemization in thiazoline derivatives.

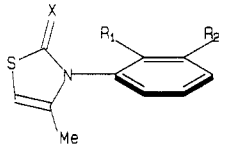
Steric barriers in biphenyl derivatives have been a cornerstone of early conformational analysis and of quantitative treatment of steric effects.[1] In biphenyl derivatives, racemization of atropisomers occurs by a rotation around the pivot bond no matter what the minute modification of the sp^2 character of the bonding atoms in the transition state. In heterocyclic analogues of biphenyl, which afford, in principle, a large variety of geometrical situations of the utmost interest for the study of steric effect,[2] one has to take into account, however, the particular structure of the heterocycle in order to clearly identify the racemization process. We report in this paper an example in which rotation about the pivot bond is not directly responsible of the observed barrier to racemization.

1-(2′-Methylphenyl)-4,6-dimethylpyrimidine-2-thione (**1a**) and 3-(2′-methylphenyl)-4-methylthiazoline-2-thione (**2a**) display the same steric pattern in the proximity of the N sp^2–C_{aryl} sp^2 bond, and the difference in the steric barriers to rotation about this bond should be related to the difference in geometry (bond lengths and internal angles) when one compares a six-membered ring to a five-membered ring.



X = S 1a

X = O 1b



X	R_1	R_2	Cpd
S	Me	H	2a
O	Me	H	2b
S	Me	Me	3a
O	Me	Me	3b
S	Me	Cl	4a
O	Me	Cl	4b
S	Cl	H	5a
O	Cl	H	5b

Kashima and Katoh[3] have reported the optical resolution of the atropisomers of **1a** by recrystallizing the salts obtained with D-camphor-10-sulfonic acid and the experimental barrier to rotation was determined ($\Delta G^{\ddagger}$ = 115.8 kJ mol^{-1}). We have estimated the barrier to rotation in **2a** to be larger than 134 kJ mol^{-1} [4] since this compound decomposes before any apparent racemization after prolonged heating at 100 °C. These results deserve further studies since one expects a larger barrier in **1a** than in **2a**.

Furthermore, Kashima and Katoh[3] found a higher racemization barrier in pyrimidone **1b** than in pyrimidinethione **1a** and proposed an attractive explanation based on a "greater single-bond character (of the thiocarbonyl group which) would probably promote bond bending..." in the sulfur derivative. Our experience on the difference in effective size of sulfur and oxygen gained through the experimental determination of the barrier to rotation of the *N*-isopropyl group in *N*-isopropyl-4-isopropyl-5-methylthiazoline-2-thione and the corresponding thiazolinone indicates a larger steric requirement of the thiocarbonyl group.[5]

We report in this paper a comparative study of racemization rates of atropisomers of **1a**, **1b**, **2a**, **2b**, and analogues separated by liquid chromatography on microcrystalline cellulose triacetate as well as X-ray structure determinations of **1a** and **3a** leading to the conclusion that the observed racemization rates for pyrimidine derivatives **1a** and **1b** reflect a reversible ring opening–ring closure reaction rather than an internal rotation around the N sp^2–C_{aryl} sp^2 bond in the pyrimidine form. Internal rotation does account for the racemization in thiazoline derivatives.

Results and Discussion

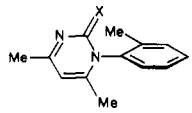
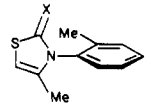
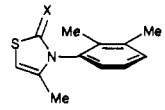
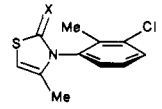
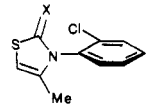
The two pyrimidine derivatives **1a** and **1b** were prepared according to ref 3. Δ^4-Thiazoline-2-thiones **2a**, **3a**, **4a**, and **5a** were prepared by reacting the appropriate dithiocarbamate with chloroacetone.[4] Thiazolinones **2b**, **3b**, **4b**, and **5b** were obtained in good yields by treatment of the corresponding thiones with methyl iodide and powdered sodium methylate in MeOH.

Liquid chromatography on microcrystalline cellulose triacetate (15–25 μm) monitored by a UV detector and a polarimeter afforded enriched samples of atropisomers of the studied compounds.[4,6] Analytical injections of further

(1) Adams, R.; Yuan, H. C. *Chem. Rev.* **1933**, *12*, 161. Adams, R. *Rec. Chem. Progr.* **1949**, 91.
(2) Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, *43*, 173–299.
(3) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599–1602.
(4) Roussel, C.; Djafri, A. *Nouv. J. Chim.* **1986**, *10*, 399–404.
(5) Liden, A.; Roussel, C.; Chanon, M.; Metzger, J.; Sandström, J. *Tetrahedron Lett.* **1974**, 3629–3632.
(6) Hesse, G.; Hagel, R. *Justus Liebigs Ann. Chem.* **1976**, 996. Hesse, G.; Hagel, R. *Chromatographia* **1976**, *9*(2), 62. Souter, R. W. In *Chromatographic Separations of Stereoisomers*; CRC: Boca Raton, FL, 1985. Mannschreck, A.; Koller, H.; Wernicke, R. *Kontakte (Darmstadt)* **1985**, *1*, 40. Blaschke, G. *J. Liq. Chromatog.* **1986**, *9*(2–3), 341. Shibata, T.; Okamoto, I.; Ishii, K. *J. Liq. Chromatogr.* **1986**, *9*(2–3), 313. Hussenius, A.; Isaksson, R.; Matsson, O. *J. Chromatogr.* **1987**, *405*, 155. Isaksson, R.; Roschester, J. *J. Org. Chem.* **1985**, *50*, 2519. Francotte, E.; Lohmann, D. *Helv. Chim. Acta* **1987**, *70*, 1569. Lienne, M.; Caude, M.; Tambute, A.; Rosset, R. *Analusis* **1987**, *15*, 431. Pirkle, W. H.; Hamper, B. C. *Journal of Chromatography Library*; Bidlingmeyer, B. A., Ed.; Elsevier: New York, 1987; Vol. 38, pp 235–288. Wainer, I. W. *Trends Anal. Chem.* **1987**, *6*, 125.

0022-3263/88/1953-5076$01.50/0

Table I. Capacity Factors and Separation Factors of Compounds 1a–5a and 1b–5b Atropisomers on Chiral Stationary Phase Microcrystalline Cellulose Triacetate (15–25 μm; Temperature 25 °C, Flow Rate 138 mL/h, Eluent Ethanol/Water, 96/4)

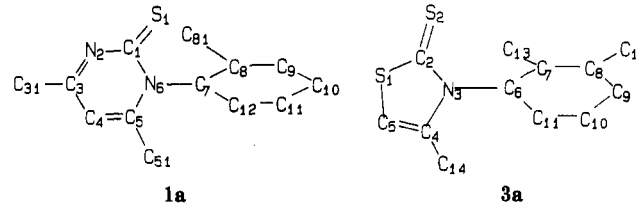
compound	no.	X	k_1	k_2	α	no.	X	k_1	k_2	α
	**1a**	S	0.37 (–)	0.39	1.045	**1b**	O	0.13 (–)	0.17	1.25
	**2a**	S	1.52 (+)	2.30	1.51	**2b**	O	1.66 (–)	2.05	1.24
	**3a**	S	0.96 (+)	3.09	3.20	**3b**	O	0.81 (+)	1.92	2.36
	**4a**	S	1.17 (+)	4.83	4.14	**4b**	O	1.42 (+)	4.29	3.01
	**5a**	S	2.09 (–)	2.18	1.04	**5b**	O	1.54 (–)	2.80	1.82

enriched samples obtained with a recycling technique allowed the determination of the capacity factors of the different enantiomers. These capacity factors, listed in Table I, were determined on a 200 mm × 25 mm column (thermostated at 25 °C) with a 138 mL/h flow rate of ethanol/water, 96/4 (pressure drop 1.65 bar). 1,3,5-Tri-*tert*-butylbenzene was used as reference.[7] All the compounds were totally or partially separated on cellulose triacetate. Pyrimidine derivatives **1a** or **1b** are less retained on the chiral stationary phase than the thiazoline compounds. The separations are strongly dependent on the substitution pattern; however, these separations on cellulose triacetate afforded in all cases enriched samples suitable for kinetic runs.

Carefully purified diglyme was used in all the kinetics of racemization. The kinetic data were obtained by monitoring the decrease of the rotatory power at the given temperature and the data treated according to a first-order model as it is usual for racemization processes.[4] In all cases in which racemization occurred, good first-order plots were obtained. However, some experimental difficulties were encountered in the kinetic studies of the pyrimidine derivatives since a strong coloration of the solutions, which developed rapidly under warming, prevented any direct measurement of the rotatory power in the polarimeter cell. It was thus necessary to perform the kinetics in sealed tubes, the resulting samples were purified by filtration on norit and alumina, and the amount of compound was determined by UV calibration. Sealed tubes were also used for slow kinetics such as for compounds **3b**, **4b**, and **5b**. The parameters for racemization processes together with those given in ref 3 are listed in Table II. We were not able to determine the racemization rate for thiazolinethione derivatives since these compounds showed no racemization but extensive decomposition under heating at 100–110 °C in diglyme. The decomposition can be easily followed by UV (decrease of the ca. 320-nm transition band); the remaining amount of thiazoline-2-thione showed no racemization according to analytical liquid chromatography on cellulose triacetate, and thus a barrier larger than 134 kJ mol^{-1} can be estimated from these data.

(7) Koller, H.; Rimbock, K. H.; Mannschreck, A. *J. Chromatogr.* **1983**, *282*, 89.

Chart I



1a **3a**

Our kinetic determinations confirmed the experimental data obtained by Kashima and Katoh,[3] i.e. the observed fading of optical activity is faster for **1a** than for **1b**; however, the absolute values we obtained are different from those given in ref 3. The reported values for **1a** and for **1b** were $\Delta G^{\ddagger}$ = 115.8 and 126.6 kJ mol^{-1}, respectively, whereas we found 107.7 and 118.2 kJ mol^{-1} in diglyme. There is no indication of the solvent in which the racemizations were performed in ref 3, and we believe that the observed differences might arise from solvent effect. Thus under identical conditions the experimental barriers are

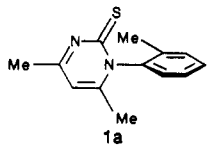
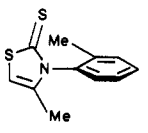
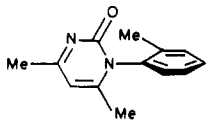
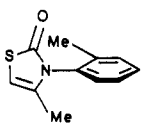
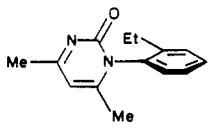
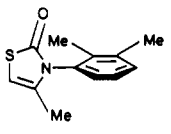
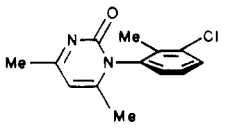
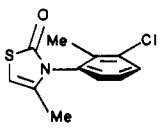
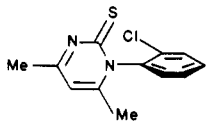
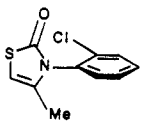
$$\mathbf{1a} < \mathbf{1b} < \mathbf{2b} < \mathbf{2a}$$

X-ray analysis of racemic pyrimidinethione **1a** and thiazolinethione **3a**[8] were performed in order to obtain informations about the structural differences within the two heterocycles. View of the **1a** and **3a** molecules and the atomic numbering schemes are presented in Chart I. The atomic coordinates and equivalent thermal parameters of non-hydrogen atoms and the bond distances and angles are listed in the supplementary material.

In both molecules, the heterocyclic framework is planar and the nitrogen atom attached to the aryl ring is a typical sp^2 hybridized atom as it is clearly shown by the sum of the interbond angles, which is equal to 360°. The interring angles between the heterocycle and the aryl group are 81.5° and 84.2°, respectively, in **1a** and **3a**. In the crystal, the same helicity is observed for the two molecules, the methyl group in ortho position of the aryl ring is slightly directed toward the thiocarbonyl group. The C=S bonds are respectively equal to 1.655 and 1.676 Å in **3a** and **1a**. These values are as expected for such compounds,[9] and fur-

(8) Compound **3a** was chosen as a model of **2a** since it gives particularly nice crystals.

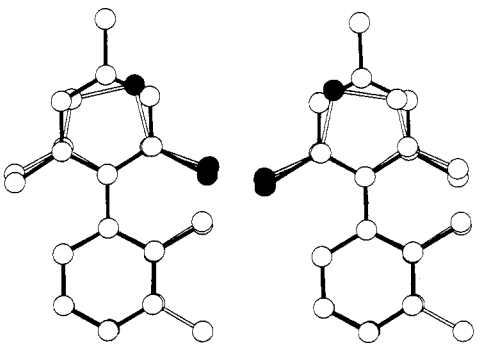
Table II. Experimental Free Energy of Activation for Racemization Processes in Pyrimidine and Thiazoline Derivatives, in Diglyme

compound	T, K	$\Delta G^{\ddagger}$, kJ mol^{-1}	compound	T, K	$\Delta G^{\ddagger}$, kJ mol^{-1}
 1a	334.7	107.7, 115.8 (ref 3)	 2a	373	>134
 1b	359.6	118.2, 126.6 (ref 3)	 2b	359	122.0
 6b		126.2 (ref 3)	 3b	360.1	130.9
 7a		112.8 (ref 3)	 4b	360.1	128.5
 8a		111.2 (ref 3)	 5b	360.1	126.9

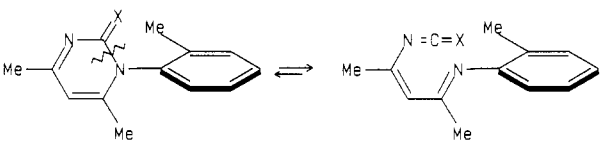
thermore the C=S bond in **1a** is at the lower limit to those recently determined in various *N*-phenylimidazoline-2-thione derivatives.[10] It thus appears that the hypothesis[3] of an exceptional single bond character of the C=S bond in **1a**, which might account for the exceptionally low racemization energy in this compound, is ruled out by the X-ray analysis. The X-ray data reveal in **1a** a particularly long bond (1.404 Å) between the carbon of the thiocarbonyl group and the *N*-aryl nitrogen. This fact, as it will be discussed later, might indicate a weak link in the molecule.

At this point of the discussion, it was particularly interesting to compare the geometries of the hypothetical planar transition states to rotation expected for a racemization process through rotation about the nitrogen–aryl bond. Two unequally populated isomeric transition states are possible, one in which the methyl group passes in front of the exocyclic sulfur or oxygen atom and the other in which the methyl group passes in front of the methyl group of the heterocycle. These two transition states have to be considered. Starting from the X-ray coordinates, we have rotated the aryl group in such a way as to simulate these two transition states in compounds **1a** and **3a** and by using the best-fit facilities the hypothetical transition states were superimposed.[11] In both transition states, the calculated

Chart II. Comparison of Idealized Isomeric Planar Transition States to Rotation Around the N sp^2–C$_{aryl}$ sp^2 Bond in 1a and 3a. The Light Bonds Are Those of 3a; (●) Sulfur Atoms



Scheme I



distances of the interacting groups are shorter in **1a** than in **3a** as shown in Chart II and thus it is clear that the barrier should be larger in the former.[12]

(9) 3-Phenylthiazolidine-2-thione: Nuzzo, O.; Pierrot, M.; Baldy, A.; Chanon, M.; Chanon, F. *Can. J. Chem.* **1984**, *62*, 1410. 5-(Methylthio)-1,3,4-thiadiazole-2-thione: Puranik, V. G.; Tavale, S. S.; Row, T. N. G.; Umapathy, P.; Budhkar, A. P. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 593. 4-(4′-Chlorophenyl)-4-thiazoline-2-thione: Nalini, V.; Desiraju, G. R. *Tetrahedron*, **1987**, *43*, 1313–1320.

(10) Moreno, E.; Lopez-Castro, A.; Marquez, R. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *C41*, 767; 1465. Criado, A.; Conde, A.; Marquez, R. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *C41*, 1215.

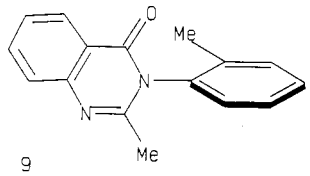
(11) All these transformations were performed by computer with use of the Chemical Graphic facilities of the Chemical Center University of Lund and those of the CRMC2, University Aix-Marseille II. We are indebted to Drs. T. Liljefors, R. E. Carter, and G. Pepe for their help.

(12) We are aware the use of this overlapping method is a rough estimation of what might be the actual geometry of the transition state. However, this method has been used with some success in predicting the barriers to rotation in biphenyl systems. Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 35. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618. Crossley, M. J.; Field, L. D.; Forster, A. J.; Harding, M. M.; Sternhell, S. *J. Am. Chem. Soc.* **1987**, *109*, 341. Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 1107. Since the same atoms in the same hybridization states are involved in the interacting part of the two molecules, molecular mechanics calculations would give the same barrier order as the overlapping method.

All these arguments lead us to propose two different mechanisms for the racemization processes in **1a** and **2b**, namely a reversible ring opening–ring closure in **1a** and a true rotation in thiazoline derivatives. In **1a** and **1b**, a thermal 3,3-electrocyclic reaction might occur by breaking of the carbon–nitrogen bond, which was found particularly longer than expected in the X-ray analysis. Such an electrocyclic reaction (Scheme I) performed on an optically enriched sample leads to an achiral fully conjugated form, which would recyclize to give the racemic form.[13] A strong argument in favor of such a process is the comparison of the effect of substitution in "buttressing" positions on the aryl ring in pyrimidine versus thiazoline derivatives. Kashima and katoh[3] reported a lower racemization energy for **7a** (112.8 kJ mol^{-1}) than the one given for **1a** (115.8 kJ mol^{-1}) (Table II). In thiazoline derivatives, a normal buttressing effect is observed under substitution in meta position by a methyl or a chloride (Table II, **2b** versus **3b** and **4b**).[3b] The observed difference in the barriers for **3b** and **4b** results from the difference in electron accepting–donating abilities of a chloride compared to a methyl as we have already shown[4] in thiazoline series. The observed high barrier in **5b** results from the direct electrostatic repulsion of the two electron-rich atoms (chloride and carbonyl oxygen) in the planar transition state.

Another argument in favor of the ring-opening process depicted in Scheme I comes from the fact that the racemization energy is unaffected by the replacement of the *o*-methyl by an ethyl group (Table II, **1b** versus **6b**), pointing out the insensibility of the process to direct steric modification.

Finally, Mannschreck et al.[14] have determined the barrier to racemization in methaqualone derivative **9** ($\Delta G^{\ddagger}$ = 131.6 kJ mol^{-1} in diphenyl ether), which displays a similar steric pattern as in **1b** ($\Delta G^{\ddagger}$ = 118.2 kJ mol^{-1} in diglyme), and in which the electrocyclic reaction depicted in Scheme I is impossible. We propose that a value close



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to 132 kJ mol^{-1} would be a realistic one for the actual rotation around the N–C_{aryl} bond in **1b**, whereas the expected value for **1a** would be larger than 150 kJ mol^{-1}.

Experimental Section

Apparatus. NMR spectra were recorded on a Bruker AM-200 spectrometer; MS spectra were obtained on a AEI 50 instrument (Kratos Ltd.); UV spectra were obtained on a Beckman Model 25 instrument; a LKB 2138 Uvicord and a Perkin-Elmer 241 C polarimeter were used as on-line detectors for chromatography.

Synthesis. 1-(2′-Methylphenyl)-4,6-dimethylpyrimidine-2-thione (1a) has been prepared by reacting *o*-tolylthiourea with 2,4-pentanedione.[3] 2,4-Pentanedione (1.15 g, 11.5 mmol) and *o*-tolylthiourea (1.43 g, 8.63 mmol) are stirred in 15 mL of ethanol (96%) until complete dissolution of the thiourea. A solution of hydrochloric acid 35% (2.15 mL) is added, and the mixture is refluxed for 3 h. After cooling, a solution of NaOH (1 g in 50 mL of water) is added with stirring. A yellow precipitate of **1a** is readily formed and washed with ethanol (0.677 g) (mp 205–6 °C, lit.[3] mp 195 °C dec). The filtrate is extracted with dichloromethane, and the crude evaporated mixture is chromatographed on silica with MeOtBu as eluent. In these conditions, **1a** is retained on the column. After elution with ethanol, evaporation, and chromatography on silica with a mixture of $CHCl_3$/acetone/EtOH (100/10/2) as eluent, a new crop of pure **1a** (1.140 g) is obtained. Total yield in **1a** 91.5%. ^{1}H NMR ($CDCl_3$): δ 1.95 (3 H, s), 2.11 (3 H, s), 2.43 (3 H, s), 6.60 (1 H, s), 7.07 (1 H, m), 7.35 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 183.67 (C=S), 169.8, 157.57, 140.19, 133.85, 131.84, 129.5, 127.98, 126.49, 111.16, 25.04, 21.85, 17.33. MS (70 eV), *m/e* (percent): 230 (53), 229 (9), 215 (50), 198 (15), 197 (100), 182 (10), 91 (53), 89 (15), 83 (17), 82 (10), 77 (11), 67 (12), 63 (14), 51 (17), 45 (12). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.83; H, 6.09; N, 12.17; S, 13.91. Found: C, 67.81; H, 6.08; N, 12.16; S, 13.9.

1-(2′-Methylphenyl)-4,6-dimethylpyrimidin-2-one (1b) was prepared by transformation of **1a** with MeONa in MeOH and treatment with methyliodide according to ref 15. Yield 80.6%. MP: 132–3 °C in agreement with ref 6. ^{1}H NMR ($CDCl_3$): δ 1.87 (3 H, s), 2.11 (3 H, s), 2.36 (3 H, s), 6.17 (1 H, s), 7.1–7.35 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 176.09 (C=O), 156.93, 156, 136.77, 134.89, 131.54, 129.40, 127.57, 127.22, 105.41, 25.32, 20.59, 17.26. MS (70 eV), *m/e* (percent): 214 (51), 200 (15), 199 (100), 197 (10), 171 (12), 144 (23), 130 (16), 91 (65), 89 (13), 77 (12), 65 (56), 63 (15), 51 (18), 42 (16), 41 (13). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.90; H, 6.54; N, 13.08. Found: C, 72.76; H, 6.6; N, 13.05.

General Procedure for the Preparation of Thiazoline-2-thiones and Thiazolin-2-ones. 3-Aryl-Δ^4-thiazoline-2-thiones were obtained by reaction of the corresponding ammonium *N*-aryldithiocarbamates obtained from carbon disulfide and the corresponding commercially available anilines[16] on 1-chloropropan-2-one in ethanol. The reaction was monitored by TLC (silica, Merck Kieselgel 60) and UV. The thiazoline-2-thiones **2a–5a** exhibit an intense UV absorption at ca. 320 nm in ethanol whereas the starting material or the open-chain intermediates have no band in this region.[17] The crude resulting oils or the pasty solids were purified by LC on silica (Merck Kieselgel 60, 0.063–0.2 mm) with a toluene/ethanol mixture (99/1) as eluent and further recrystallized from 95% ethanol. No attempts to optimize the yields were performed.

3-Aryl-Δ^4-thiazolin-2-ones 2b–5b were prepared in good yields from the corresponding thione derivatives (1 mmol) by treatment with MeONa (4 mmol) in methanol (20 mL) and methyliodide (10 mmol) at room temperature with stirring. At the end of the reaction (15–24 h as monitored by TLC on silica eluent chloroform), water (20 mL) was added and the medium was extracted with dichloromethane. After drying, evaporation, and LC on silica (eluent $CHCl_3$), the thiazolin-2-ones were obtained in pure state.

3-(2′-Methylphenyl)-4-methyl-Δ^4-thiazoline-2-thione (2a). Yield 60%, mp 118 °C (ammonium 2-methylphenyl dithiocarbamate: yield 73%, mp 92 °C). ^{1}H NMR ($CDCl_3$): δ 1.89 (3 H, d, J = 1.14 Hz), 2.12 (3 H, s), 6.38 (1 H, q, J = 1.14 Hz), 7.13 (1 H, m), 7.39 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 189.27 (C=S), 139.74 (C4), 136.93, 136.15, 131.56, 129.98, 128.13, 127.56, 106.40 (C5), 17.32, 15.68 (4-Me). MS (70 eV), *m/e* (percent): 222 (8), 221 (61), 206 (29), 189 (14), 188 (100), 187 (14), 173 (7), 109 (7), 91 (30), 89 (12), 77 (8), 72 (7), 71 (15), 61 (26), 51 (11), 39 (27). UV (EtOH): λ_{max} (ϵ) 327.4 (12 300), 212 (18 500). Anal. Calcd for $C_{11}H_{11}NS_2$: C, 59.73; H, 4.98; N, 6.33; S, 28.96. Found: C, 59.5; H, 4.90; N, 6.23; S, 28.9.

3-(2′,3′-Dimethylphenyl)-4-methyl-Δ^4-thiazoline-2-thione (3a). Yield 70%, mp 90 °C (ammonium 2,3-dimethylphenyl dithiocarbamate: yield 93%, mp 76 °C). ^{1}H NMR ($CDCl_3$): δ 1.88 (3 H, s), 1.97 (3 H, s), 2.36 (3 H, s), 6.37 (1 H, s), 6.98 (1 H, m), 7.27 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 189.22 (C=S), 140.04 (C4), 138.90, 136.86, 134.53, 131.34, 126.84, 125.56, 106.28 (C5), 20.25, 15.69 (4-Me), 13.81. MS (70 eV), *m/e* (percent): 235 (84), 220 (48), 202 (100), 187 (30), 105 (11), 103 (11), 91 (6), 77 (22),

(13) The open form reported in Scheme I is closely related to the possible intermediate of the synthesis of *N*-arylpyrimidinethiones from 3-(isothiocyanato)-2-propeniminium perchlorates and aryl amines: Katoh, A.; Nishio, T.; Kashima, C. *Heterocycles* **1987**, *26*, 2223.

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71 (9), 51 (10), 45 (11), 39 (15). UV (EtOH): λ_{max} (ϵ) 326 (10500), 210 (18500). Anal. Calcd for $C_{12}H_{13}NS_2$: C, 61.3; H, 5.5; N, 6.0; S, 27.2. Found: C, 61.08; H, 5.69; N, 5.92; S, 27.

3-(3′-Chloro-2′-methylphenyl)-4-methyl-Δ⁴-thiazoline-2-thione (4a). Yield 30%, mp 104 °C (ammonium 3-chloro-2-methylphenyl dithiocarbamate: yield 75%, mp 100 °C). ^{1}H NMR ($CDCl_3$): δ 1.89 (3 H, d, J = 1.11 Hz), 2.12 (3 H, s), 6.39 (1 H, q, J = 1.11 Hz), 7.05–7.57 (3 H, complex). ^{13}C NMR ($CDCl_3$): δ 189.55 (C=S), 139.48 (C4), 138.21, 136.27, 135.12, 130.82, 127.85, 127.06, 106.62 (C5), 15.62 (4-Me), 14.84. MS (70 eV), m/e (percent): 257 (28), 255 (85), 242 (17), 240 (47), 224 (48), 222 (88), 187 (100), 125 (26), 99 (14), 90 (14), 89 (60), 77 (14), 71 (41), 64 (43), 51 (23), 45 (11), 39 (15). UV (EtOH): λ_{max} (ϵ): 327.2 (13000), 212 (22500). Anal. Calcd for $C_{11}H_{10}ClNS_2$: C, 51.6; H, 3.90; N, 5.48; S, 25.05; Cl, 13.89. Found: C, 51.7; H, 4.07; N, 5.48; S, 25; Cl, 13.7.

3-(2′-Chlorophenyl)-4-methyl-Δ⁴-thiazoline-2-thione (5a). Yield 15%, mp 150 °C (ammonium 2-chlorophenyl dithiocarbamate: yield 63%, oil). ^{1}H NMR ($CDCl_3$): δ 1.94 (3 H, s), 6.39 (1 H, s), 7.25–7.65 (4 H, complex). ^{13}C NMR ($CDCl_3$): δ 190.19 (C=S), 139.56 (C4), 135.67, 132.92, 131.19, 130.93, 130.58, 128.36, 106.30 (C5), 15.39 (4-Me). MS (70 eV), m/e (percent): 243 (5), 241 (14), 208 (8), 207 (14), 206 (100), 111 (11), 75 (14), 71 (10), 45 (11), 39 (8). UV (EtOH): λ_{max} (ϵ) 327 (21300), 214 (37000). Anal. Calcd for $C_{10}H_8ClNS_2$: C, 49.7; H, 3.31; N, 5.80; S, 26.5; Cl, 14.7. Found: C, 49.36; H, 3.43; N, 5.95; S, 26.5; Cl, 15.

3-(2′-Methylphenyl)-4-methyl-Δ⁴-thiazolin-2-one (2b). Yield 94%, mp 115–6 °C. R_f ($CHCl_3$) 0.20. ^{1}H NMR ($CDCl_3$): δ 1.74 (3 H, s), 2.14 (3 H, s), 5.82 (1 H, s), 6.97–7.27 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 171.95 (C=O), 136.66, 134.73, 132.40 (C4), 131.23, 129.55, 128.68, 127.16, 96.24 (C5), 17.35, 15.45 (4-Me). MS (70 eV), m/e (percent): 205 (75), 172 (59), 144 (11), 132 (100), 91 (52), 89 (10), 77 (5), 65 (29). Anal. Calcd for $C_{11}H_{11}NOS$: C, 63.4; H, 5.57; N, 7.80; S, 15.6. Found: C, 62.4; H, 5.68; N, 6.; S, 17.2.

3-(2′,3′-Dimethylphenyl)-4-methyl-Δ⁴-thiazolin-2-one (3b). Yield 85%, mp 159–160 °C. R_f ($CHCl_3$) 0.44. ^{1}H NMR ($CDCl_3$): δ 1.72 (3 H, s), 2.00 (3 H, s), 2.30 (3 H, s), 5.80 (1 H, s), 6.89–7.29 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 172.07 (C=O), 138.52, 135.04, 134.56, 132.59 (C4), 130.86, 126.38, 126.11, 95.93 (C5), 20.24, 15.40 (4-Me), 13.64. MS (70 eV), m/e (percent): 219 (74), 204 (10), 187 (14), 186 (94), 176 (13), 158 (18), 147 (13), 146 (100), 131 (13), 105 (45), 103 (22), 91 (8), 89 (5), 79 (28), 78 (14), 77 (45), 51 (14). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.8; H, 5.9; N, 6.4; S, 14.6. Found: C, 65.75; H, 6.1; N, 6.3; S, 14.3.

3-(3′-Chloro-2′-methylphenyl)-4-methyl-Δ⁴-thiazolin-2-one (4b). Yield 78%, mp 128–129 °C. R_f ($CHCl_3$) 0.46. ^{1}H NMR ($CDCl_3$): δ 1.73 (3 H, s), 2.16 (3 H, s), 5.83 (1 H, s), 7.10–7.54 (3 H, m). ^{13}C NMR ($CDCl_3$): δ 171.84 (C=O), 135.93, 135.84, 135.46, 132.10 (C4), 130.43, 127.45 (2 C), 96.62 (C5), 15.37 (4-Me), 14.93. MS (70 eV), m/e (percent): 241 (35), 239 (90), 224 (13), 208 (31), 206 (92), 178 (15), 168 (33), 166 (100), 163 (15), 131 (29), 127 (13), 125 (41), 99 (15), 90 (16), 89 (53), 77 (9), 63 (22), 45 (18). Anal. Calcd for $C_{11}H_{10}ClNOS$: C, 55.1; H, 4.18; N, 5.85; S, 13.36; Cl, 14.9. Found: C, 55.3; H, 4.3; N, 5.85; S, 13.2; Cl, 14.7.

3-(2′-Chlorophenyl)-4-methyl-Δ⁴-thiazolin-2-one (5b). Yield 76%, mp 110–111 °C. R_f ($CHCl_3$) 0.33. ^{1}H NMR ($CDCl_3$): δ 1.82 (3 H, s), 5.86 (1 H, s), 7.19–7.60 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 171.8 (C=O), 132.18 (C4), 130.85, 130.66, 130.44, 128.09, 96.37 (C5), 15.09 (4-Me). MS (70 eV), m/e (percent): 227 (15), 225 (41), 190 (48), 162 (31), 154 (33), 152 (100), 113 (14), 111 (41), 77 (6), 76 (10), 75 (46), 45 (26). Anal. Calcd for $C_{10}H_8ClNOS$: C, 53.2; H, 3.55; N, 6.2; S, 14.2; Cl, 15.7. Found: C, 53.2; H, 3.7; N, 6.24; S, 13.9; Cl, 15.7.

Liquid Chromatography on Microcrystalline Cellulose Triacetate. Cellulose triacetate (15–25 μm from Merck) was packed in a thermostated 200 × 25-mm glass column equipped with a 5-cm^3 injection loop. UV (LKB 2138 UVICORD) and polarimetric (Perkin-Elmer 241) detections were used. In all cases the elution solvent was ethanol/water, 96/4, flow rate 138 mL/h, pressure drop ca. 1.7 bar, temperature 25 °C. For analytical runs, 2–3 mg of racemate were used in order to determine k_1 and k_2, and 1,3,5-tri-*tert*-butylbenzene was used as reference. When the separation was particularly bad, the capacity factors given in Table I were determined by separate injection of each enantiomers. Semipreparative injections were performed on 80–100-mg samples in 5–10 mL of ethanol, depending on the solubility; the flow rate in preparative injection was 98 mL/h. After three to five cycles, samples of high enantiomeric purity suitable for the determination of the capacity factors and enriched mixtures suitable for kinetic of racemization were obtained.

Kinetics of Racemization. They were performed in freshly purified diglyme[18] on enriched samples directly in the polarimeter cell or in cases of slow kinetics or partial decomposition in sealed tubes. First-order kinetics were obtained in all cases. For pyrimidine derivatives, the racemization rates are in principle high enough to be monitored directly in the polarimeter cell; however, a strong coloration of the solution, which developed rapidly with warming, resulted in a strong absorption of the energy, which did not allow the use of this simple technique. It was necessary for these compounds to perform the kinetics in the following way: a known concentration of enriched samples in diglyme was equally dispatched into 8–12 sealed tubes (2–3 mL per tube); these tubes were placed into a thermostated bath as for classical slow kinetic run. After the desired lapse of time, the contents of the tube were passed through a norit layer and neutral alumina layer to get rid of the coloration. The resulting transparent solution was studied by polarimetry, and the concentration of pyrimidine derivatives was determined by UV analysis with a calibration curve already established for the actual concentration range in diglyme. This procedure allowed the calculation of the remaining optical activity and corrected the decomposition and postkinetic treatment losses of compound. These calculated values were used for the kinetic calculations, which were performed up to 3 half-lives. The general precision of the data given in Table II is ≃0.1 kJ mol^{-1} for $\Delta G^{\ddagger}$ values. $\Delta G^{\ddagger}$ values reported in Table II correspond to the rotation process.

X-ray Determinations. Diffraction data were collected with a CAD 4 Enraf-Nonius diffractometer, Mo Kα radiation (0.71073 Å) in the "Department de Cristallochimie" of the University Aix-Marseille III. Intensities were not corrected for absorption. The structures were solved and refined with the SDP software (Frenz 1978) by a combination of Patterson, difference-Fourier, and full-matrix least-squares refinement techniques using anisotropic thermal parameters for all non-hydrogen atoms.

Compound **1a** crystallizes in the monoclinic space group $p2_1/c$ with a = 9.526 (3), b = 11.557 (4), and c = 13.446 (4) Å; β = 124.2 (1)°. The final conventional residual was R = 0.048 and R_w = 0.074 for 1468 reflections and 145 variables.

Compound **3a** crystallizes in the monoclinic space group $p2_1/n$ with a = 9.750 (3), b = 8.857 (3), and 15.084 (4) Å; β = 107.16°. The final conventional residual was R = 0.049 and R_w = 0.059 for 2748 reflections and 136 variables.

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Registry No. (+)-**1a**, 116350-50-6; (−)-**1a**, 116350-51-7; (±)-**1a**, 116350-52-8; (+)-**1b**, 116350-53-9; (−)-**1b**, 66783-88-8; (±)-**1b**, 116350-54-0; (+)-**2a**, 116350-55-1; (−)-**2a**, 116350-56-2; (+)-**2a**, 116350-57-3; (+)-**2b**, 116350-58-4; (−)-**2b**, 116350-59-5; (±)-**2b**, 116350-60-8; (+)-**3a**, 116350-61-9; (−)-**3a**, 116350-62-0; (±)-**3a**, 116350-63-1; (+)-**3b**, 116350-64-2; (−)-**3b**, 116350-65-3; (±)-**3b**, 116350-66-4; (+)-**4a**, 116350-67-5; (−)-**4a**, 116350-68-6; (±)-**4a**, 116350-69-7; (+)-**4b**, 116350-70-0; (−)-**4b**, 116350-71-1; (±)-**4b**, 116350-72-2; (+)-**5a**, 116350-73-3; (−)-**5a**, 116350-74-4; (±)-**5a**, 116350-75-5; (+)-**5b**, 116350-76-6; (−)-**5b**, 116350-77-7; (±)-**5b**, 116350-78-8; *o*-tolylthiourea, 614-78-8; 2,4-pentanedione, 123-54-6; carbon disulfide, 75-15-0; 1-chloropropan-2-one, 78-95-5; ammonium 2-methylphenyldithiocarbamate, 52908-85-7; 2-methylbenzenamine, 95-53-4; ammonium 2,3-dimethylphenyl dithiocarbamate, 108654-37-1; 2,3-dimethylbenzenamine, 87-59-2; ammonium 3-chloro-2-methylphenyl dithiocarbamate, 116350-79-9; 3-chloro-2-methylbenzenamine, 87-60-5; ammonium 2-chlorophenyl dithiocarbamate, 66065-30-3; 2-chlorobenzenamine, 95-51-2.

Supplementary Material Available: X-ray data for **1a** and **3a** (15 pages) and structure factors for **1a** and **3a** (15 pages). Ordering information is given on any current masthead page.

(18) Purification of diglyme was performed according to the procedure described in *Vogel's Textbook of Practical Organic Chemistry*, 4th Ed.; Longman: New York, 1978; p 274.